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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,230	07/01/2005	Gijs Robert Van Den Brink	VAN DEN BRINK1	1902

1444 7590 12/05/2008

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,230	VAN DEN BRINK ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-13,25-29 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *25-29,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-13,31 and 34-38* is/are rejected.

7)☒ Claim(s) *10 and 11* is/are objected to.

8)☒ Claim(s) *1-4,6-13,25-29 and 31-38* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment to the specification filed on 5/20/08 has been entered in full. However, it is noted that Applicants submitted a non-compliant amendment (not entered) to the specification on 4/29/08, with amendments to two parts of the specification at page 1 and page 16. In the 5/20/08 amendment, only page 1 is amended. Thus, the amendment to page 16 has not been entered.

The claim amendments of 8/12/08 have been entered in full. Claims 1-4, 7-10, 12, 13 and 31 are amended. Claims 5 and 30 are canceled (claims 14-24 were previously cancelled). New claims 34-38 are added.

Claims 1-4, 6-13, 25-29 and 31-38 are pending in the instant application.

This application contains claims 25-29, 32 and 33 drawn to invention(s) nonelected with traverse in Applicants' response filed 8/27/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 25-29, 32 and 33 remain withdrawn as indicated at page 2 of the 11/1/07 Office Action.

Claims 1-4, 6-13, 31 and 34-38 are under consideration.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (11/1/07).

All objections and/or rejections of claims 5 and 30 are moot in view of Applicants' cancellation of these claims.

The objection to claims 12 and 13 at pg 3 is *withdrawn* in view of Applicants' amendments to the claims.

The rejections of claim 1 and 31 under 35 U.S.C § 112, second paragraph, at pg 14-15 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 1, 6-9 and 31 under 35 U.S.C. § 102(b) at pg 15-16 as being anticipated by Tonelli et al (1995) is *withdrawn* in view of Applicants' amendments to the claims that limit the composition of claim 1 to one that does not include the butyrate compound as taught by Tonelli et al.

Maintained Objections and/or Rejections

Specification

In the Office Action mailed on 11/1/07, the specification was objected to for two reasons. The first reason has been rendered moot by Applicants' amendment to the specification filed on 5/20/08. An amendment to the specification that would have rendered moot the second reason was included as part of a non-compliant amendment filed on 4/29/08. However, because a portion of this amendment was non-compliant, the entirety of the amendment was not entered in the record of the Application. Thus, the objection to the disclosure is maintained for the following informality:

The disclosure is objected to because it contains an embedded hyperlink at page 15, line 32. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01 (part VII).

Appropriate correction is required. This objection would be overcome if the amendment to page 16 that was included in the non-compliant amendment filed on 5/20/08 was resubmitted as part of a compliant amendment.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-11, 13, 31 and 34-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a deficiency of a Hedgehog protein in the gastrointestinal tract (GI) of an adult who has a deficiency in said protein and is in need of said treatment, comprising providing to the

GI tract of the subject in need thereof a composition that comprises a source of a Hedgehog protein, selected from the group consisting of (1) polypeptide comprising an amino acid sequence with at least 95% sequence identity to SEQ ID NO: 1, 2 or 3 and having the biological activity of binding to Hedgehog binding receptor Patched and activating signaling downstream of Patched; (2) a bacterial delivery vehicle comprising a non-pathogenic enteric bacterium, capable of colonizing the subject's GI tract, which bacterium is transformed with a expression vector encoding a polypeptide of (1); or (3) an animal cell that expresses and secretes a polypeptide of (1), and wherein providing said composition results in prevention of development of cancer of the small intestine or colon, does not reasonably provide enablement for the full scope of the method recited in claims 1, 2, 6-11, 13, 31 or 34-38. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The enablement rejection was set forth previously at pg 3-11 of the 11/1/07 Office Action, and has been amended as indicated above as necessitated by Applicants' claim amendments and response.

Applicants' arguments (4/29/08; pg 11-19) as they pertain to the rejection have been fully considered and are considered persuasive in part.

In the response, Applicants argue that "exemplary support for "preventing" is provided in the form of the van Den Brink Declaration which describes after-filing experiments that confirm what was stated in the application regarding prevention of cancer development" and "show that Shh protein expressed in, and released from transgenic enteric bacterial cells are biologically active, and that delivery of these bacteria to the G.I. tract by oral gavage results in regionally selective expression of Shh protein in mice. This expression is associated with prevention of the development of adenomatous polyps which are recognized as precursors of GI cancer" (pg 15-16). In support of these arguments, Applicants on 4/29/08 filed the Declaration Under 37 CFR § 1.132 of Gijs van Den Brink.

Applicants' arguments, and the 4/29/08 van Den Brink Declaration, have been fully considered and this portion of Applicants' arguments are found to be persuasive

with respect to the following. The Declaration describes administration of transformed *Lactococcus lactis* bacterial cells that secrete recombinant murine Sonic hedgehog (Shh) protein to mice. The results demonstrate (in normal mice) that Shh "significantly increased the concentration of total hedgehog protein in the distal small intestine (as compared to the proximal duodenum), with the highest concentration in the ileum" (pg 2). The results further demonstrate that administration of said bacteria to a mouse model of colon cancer development "was found to prevent adenoma formation in the ileum (highly statistically significant)" (pg 2). The relevant art teaches that the "Apc mouse models have been shown to be relevant models for evaluating human chemopreventative therapies" (pg 479 of McCart et al, 2008. Pathology - Research and Practice. 204: 479-490). Furthermore, use of *L. lactis* to successfully deliver a secreted gene product to the GI tract was taught in the prior art (see page 181 of Steidler et al, 2006. Ann NY Acad Sci. 1072: 176-186). The specification includes the genus *Lactococcus* among the preferred enteric bacteria to be used in the instant invention. Furthermore, Shiotani et al (2005) teach that "loss of Shh in H. Pylori-associated gastritis is an early change that occurs in the mucosa prior to cellular transformation and correlated with IM [intestinal metaplasia]. Shh plays an important role in sustaining gastric epithelia differentiation and the loss of Shh may be involved in carcinogenesis at an early stage" (pg 586 of Shiotani et al, 2005. American Journal of Gastroenterology. 100: 581-587). These teachings support the results found in example 2.1 of the specification that Shh protein expression is lost in areas of intestinal metaplasia ("replacement of gastric epithelium by epithelium of intestinal phenotype" and a "risk factor for development of gastric adenocarcinoma"; pg 38). In view of the results described in the Declaration, and the teachings of the relevant art, the instant specification provides enablement for a method of treating a deficiency of a Hedgehog protein in the gastrointestinal tract (GI) of an adult who has a deficiency in said protein and is in need of said treatment, comprising providing to the GI tract of the subject in need thereof a composition that comprises a source of a Hedgehog protein, selected from the group consisting of (1) polypeptide comprising an amino acid sequence with at least 95% sequence identity to SEQ ID NO: 1, 2 or 3 and having the biological activity of

binding to Hedgehog binding receptor Patched and activating signaling downstream of Patched; (2) a bacterial delivery vehicle comprising a non-pathogenic enteric bacterium, capable of colonizing the subject's GI tract, which bacterium is transformed with a expression vector encoding a polypeptide of (1); or (3) an animal cell that expresses and secretes a polypeptide of (1), and wherein providing said composition results in prevention of development of cancer of the small intestine or colon.

However, the rejection is maintained for the following reasons:

(1) While the specification enables the claimed methods with regard to "prevention of development of cancer of the small intestine or colon" it does not provide enablement for "therapy of cancer of the small intestine or colon cancer" as recited in claim 2 and encompassed by claims 1, 6-11, 13, 31 and 34-38. The results described in the van Den Brink Declaration provide evidence that administration of Shh causes a reduced occurrence of polyp formation (which is a risk factor leading to development of cancer) but do not speak to the therapy of established cancers of the small intestine or colon. As set forth previously, the relevant art teaches that the role of hedgehog proteins in the adult human gastrointestinal tract is complex and not well understood. For example, van Den Brink (2007. Physiol Rev. 87(4):1343-75; cited previously) teaches that while Indian hedgehog “expression is lost very early in the process of colorectal carcinogenesis in humans” (pg 1368) “the relevance of the loss of Hedgehog signaling in colorectal carcinogenesis is not yet clear” (pg 1369). van Den Brink reports that different studies have provided conflicting results as to whether or not hedgehog signaling is active in colorectal cancer cells (pg 1368-1369). Importantly, van Den Brink teaches that “at later stages of carcinogenesis there is a gain of Hedgehog signaling that maintains viability of carcinoma cells” (pg 1370) and “[t]he spectacular effect of SMO inhibition on the viability of many gastrointestinal cancer cell lines suggests that the Hedgehog pathway may be an attractive target for cancer therapy” (pg 1369). These teachings highlight differences between role of the Hedgehog protein in tumorigenesis versus the maintenance and growth cancers once established. In view of the teachings of the specification and the relevant art, the skilled artisan could not predict whether administration of a Hedgehog protein (e.g., Indian) to a subject with a deficiency in a

Hedgehog protein (e.g., lack of Indian in a colon cancer) would result in therapy of a cancer of the small intestine or colon, have no effect, maintain the cancer, or stimulate cancerous growth. It would require undue experimentation to test subjects with such deficiencies to determine whether or not such treatment would effective.

(2) The claims encompass methods of treatment comprising administration of compositions comprising a genus of variant sources of a Hedgehog protein. These sources include a polypeptide comprising an amino acid sequence with at least 63% sequence identity to SEQ ID NO: 1, 2 or 3; and nucleic acid vectors, enteric bacteria and animal cells encoding said polypeptides. Claims 1, 2, 6-9, 31 and 34-38 are directed to methods that encompass each type of source as a Markush-type group. Claims 10, 11, and 13 each limit the source to one particular subgenus, i.e., variant Hedgehog polypeptides (claims 10 and 11) or an enteric bacterium said polypeptides (claim 13). As amended, the claims limit the Hedgehog protein structurally to having at least 63% sequence identity to SEQ ID NO: 1 (human Desert hedgehog), SEQ ID NO: 2 (human Indian hedgehog) or SEQ ID NO: 3 (human Sonic hedgehog) and functionally to having one of four biological activities: binding to the Patched receptor; maintaining homeostasis of adult intestinal epithelium; restores epithelia differentiation of GI tract cells, avoiding carcinogenesis; or causes GI epithelial tumorigenic cells to undergo a cell death program, avoiding carcinogenesis and allowing shedding of these cells into the GI lumen.

In the response, Applicants argue (pg 18) that the scope of the claims with respect to variant Hedgehog proteins has been substantially narrowed and now includes functional limitations. Applicants argue that it would require "no more than routine experimentation to evaluate a given polypeptide for its utility in accordance with these claims as well as its "status" as falling inside or outside the claims' scope" (pg 18).

These arguments have been fully considered but are not found to be persuasive. In the amended claims the genus of variants has been reduced, but not in a meaningful manner with respect to the undue experimentation required to make and test a representative number of species in the genus. The encompassed genus remains highly variant because a significant number of structural differences between genus

members are permitted. SEQ ID NO: 1 is 396 amino acids in length; SEQ ID NO: 2 is 293 amino acids in length; and SEQ ID NO: 3 is 462 amino acids length. Thus a protein that is at least 63% identical to SEQ ID NO: 1 tolerates up to 147 amino acid changes in combination; a protein that is at least 63% identical to SEQ ID NO: 2 tolerates up to 108 amino acid changes in combination, and a protein that at least 63% identical to SEQ ID NO: 3 tolerates up to 171 amino acid changes in combination.

To put the situation in perspective, the number of possible amino acid sequences that are 100 amino acids in length is 20^{100} (approx. 10^{130}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence (X = 19 for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}.

In the present case, the reference amino acid sequence of SEQ ID NO: 2 is 293 amino acids long. A sequence that is at least 63% identical to SEQ ID NO: 11 tolerates up to 108 amino acid changes. Therefore, the total number of possible amino acid

sequences that are at least 63% identical to SEQ ID NO: 2 equals (19^{108} * 293^{108}/108!). This value exceeds the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, while limiting the scope of potential sequences to those that are at least 63% identical to a reference sequence reduces the number of potential sequences to test (as compared to having no structural limitation at all), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which one of the recited functional activities. Even considering a much narrower genus recited in the claims, such as "at least 90% sequence identity to SEQ ID NO: 2" (which tolerates up to 29 amino acid changes in any combination (0.90 X 293 = 263.7), the total number of possible amino acid sequences is still about 4.7 x 10^{77} (19^{29} * 293^{29})/29!). Such a genus is still so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus.

Furthermore, the recited functional activities are not sufficient to identify active variants that can be used in the recited claims. First, binding to Hedgehog binding receptor Patched is not sufficient to determine a variant is an active variant. Hedgehog variants may bind to Patched, yet fail to activate the receptor; these proteins would be antagonists of the Hedgehog signaling pathway and would be work in place of deficiency of Hedgehog protein. An active variant that replaces a deficiency of Hedgehog must be able to bind to Patched and activate the receptor (i.e., activate signaling downstream of Patched). Second, the specification does not teach how to determine if a hedgehog variant "maintains homeostasis of adult intestinal epithelium"; "restores epithelial differentiation of GI tract cells, avoiding carcinogenesis"; or "causes GI epithelial tumorigenic cells to undergo a cell death program, avoiding carcinogenesis and allowing shedding of these cells into the GI tract" by any means other than performing the method of treatment as recited in the claim. Thus, the recitation of these activities fails to narrow the claims with respect to undue experimentation, because the skilled artisan must still make and test each variant in the claimed method to determine if the variant has the recited biological activity.

Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 1, 2 or 3 and variants thereof. As set forth previously, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (Wells, 1990; Ngo et al, 1995; each cited previously). However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Wells (1990); Ngo (1995); Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(3) As amended, claims 1, 2, 6-9, 31 and 34-38 each encompass treatment by administration of a nucleic acid that encodes a Hedgehog protein or variant thereof. However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced to an organism by administration and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; cited previously). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art

may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In the response, Applicants argue that "the art is replete with teachings of expression vectors of various types (plasmid, bacterial, viral, liposomes, etc) that result in either transient or stable, constitutive or inducible protein expression in vivo after administering the vectors. Therefore, it is within the skill of the art to use the claimed nucleic acid embodiments as "sources of the Hedgehog polypeptides" to achieves objectives of the claimed methods without undue experimentation or further inventive effort".

Applicants' arguments have been fully considered but are not found persuasive. Applicants provide arguments, but no evidence, in support of the contention that the claimed methods are enabled with respect to administration of nucleic acids (gene therapy). The Examiner cited Philips (2001) as teaching that gene therapy has been inadequate to achieve a meaningful clinical response. Applicants argue that the art teaches protein expression in vivo following administration of nucleic acids, but do not provide any evidence of predictable treatment using such. Therefore, it is maintained that undue experimentation would be required to introduce and express the claimed nucleic acid into the cell of an organism to treat a disease.

Claims 3, 4 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3, 4 and 12 are limited to a particular embodiment that was indicated as lacking enablement in the rejection set forth above. In particular claims 3 and 4 are limited to methods providing "therapy of small intestine or colon cancer carcinoma" (claim 3) or wherein "the cancer is a carcinoma and providing of said composition results in therapy of said carcinoma" (claim 4). Thus, these claims are limited to an embodiment that was indicated as lacking enablement in part (a) of the rejection set forth above. Claim 12 is limited to a gene therapy method; specifically, the method of claim 1, "wherein the source of the Hedgehog protein is a pharmaceutical composition comprising said nucleic acid vector or (b)". Thus, this claim is limited to an embodiment that was indicated as lacking enablement in part (c) of the rejection set forth above. Thus, the rejection of these claims is maintained for the reasons set forth above.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4, 6-13, 31 and 34-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 11-14 of the 11/1/07 Office Action for claims 1-4, 6-13 and 31; new claims 34-38 are herewith included in this rejection.

Applicants' arguments (4/19/08; pg 19-22) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

At the top of page 19, Applicants argue that that the combination of structural and functional limitations are sufficient for the skilled artisan to recognize that Applicants were in possession of the claimed invention at the time of filing. This argument is further elaborated at pages 21-22, where Applicants argue that the burden for a prima facie case of inadequate written description has not been met. Applicants argue that the

scope of the claims has been substantially narrowed and is now "limited to those with at least 63% sequence identity to three specific sequences" and includes "functional limitations that further limit the scope of the genus of polypeptides" (pg 22). Applicants characterize the function of the written description requirement and point to *In re Smith* (1978); *In re Lukach* (1971); *In re Smythe* (1973); *Ralston Purina Co. v. Far-Mar-Co, Inc.* (1985) and *Vas-Cath Inc v. Mahurkar* (1991). Applicants further point to *In re Wertheim* in support of the argument that "the description requirement does not require that the specification describe the claim limitations exactly, but only so clearly that the persons of ordinary skill in the art will recognize from the disclosure that Applicant's invention includes those limitations".

Applicants' arguments have been fully considered but are not found persuasive. Applicants' characterization of *In re Smith*, *In re Lukach*, *In re Smythe*, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, *Vas-Cath Inc v. Mahurkar,* and *In re Wertheim* is not disputed. However, the rejection set forth previously and maintained herein satisfied the burden of presenting reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The instant claims are directed to methods that require use of a genus of "hedgehog proteins"; thus, satisfying the written description requires describing the genus of hedgehog proteins to be used.

In the amended claims the genus of variants has been reduced, but not in a meaningful manner when comparing the size of the encompassed genus to be described to the three functional species disclosed in the specification (SEQ ID NO: 1, 2 and 3). The encompassed genus remains highly variant because a significant number of structural differences between genus members are permitted. SEQ ID NO: 1 is 396 amino acids in length; SEQ ID NO: 2 is 293 amino acids in length; and SEQ ID NO: 3 is 462 amino acids length. Thus a protein that is at least 63% identical to SEQ ID NO: 1 tolerates up to 147 amino acid changes in combination; a protein that is at least 63% identical to SEQ ID NO: 2 tolerates up to 108 amino acid changes in combination, and a protein that at least 63% identical to SEQ ID NO: 3 tolerates up to 171 amino acid changes in combination.

To put the situation in perspective, the number of possible amino acid sequences that are 100 amino acids in length is 20^{100} (approx. 10^{130}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence (X = 19 for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}.

In the present case, the reference amino acid sequence of SEQ ID NO: 2 is 293 amino acids long. A sequence that is at least 63% identical to SEQ ID NO: 11 tolerates up to 108 amino acid changes. Therefore, the total number of possible amino acid sequences that are at least 63% identical to SEQ ID NO: 2 equals ($19^{108} * 293^{108}/108!$). This value exceeds the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, while limiting the scope of potential sequences to those that are at least 63% identical to a reference sequence reduces the number of potential sequences to test (as compared to having no structural limitation at all), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of

impossibility of making and testing sequences for those which one of the recited functional activities. Even considering a much narrower genus recited in the claims, such as "at least 90% sequence identity to SEQ ID NO: 2" (which tolerates up to 29 amino acid changes in any combination (0.90 X 293 = 263.7), the total number of possible amino acid sequences is still about 4.7×10^{77} ($19^{29} * 293^{29}$)/29!). Such a genus is still so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus.

Furthermore, the recited functional activities are not sufficient to identify active variants that can be used in the recited claims. First, binding to Hedgehog binding receptor Patched is not sufficient to describe a variant that is an active variant. Hedgehog variants may bind to Patched, yet fail to activate the receptor; these proteins would be antagonists of the Hedgehog signaling pathway and would be work in place of deficiency of Hedgehog protein. An active variant that replaces a deficiency of Hedgehog must be able to bind to Patched and activate the receptor (i.e., activate signaling downstream of Patched). Second, the specification does not teach how to determine if a hedgehog variant "maintains homeostasis of adult intestinal epithelium"; "restores epithelial differentiation of GI tract cells, avoiding carcinogenesis"; or "causes GI epithelial tumorigenic cells to undergo a cell death program, avoiding carcinogenesis and allowing shedding of these cells into the GI tract" by any means other than performing the method of treatment as recited in the claim. Thus, the recitation of these activities fails to narrow the claims with respect to description of the genus of variants, because there is no description of what variations can be made in the hedgehog protein and still retain these functionalities.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide

sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides, nucleic acids, cells, molecules or agents. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See

Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of treating a deficiency of a Hedgehog protein in the gastrointestinal tract (GI) of an adult who has a deficiency in said protein and is in need of said treatment, comprising providing to the GI tract of the subject in need thereof a composition that comprises a source of a Hedgehog protein, selected from the group consisting of (1) polypeptide comprising an amino acid sequence with at least 95% sequence identity to SEQ ID NO: 1, 2 or 3 and having the biological activity of binding to Hedgehog binding receptor Patched and activating signaling downstream of Patched; (2) a bacterial delivery vehicle comprising a non-pathogenic enteric bacterium, capable of colonizing the subject's GI tract, which bacterium is transformed with a expression vector encoding a polypeptide of (1); or (3) an animal cell that expresses and secretes a polypeptide of (1), and wherein providing said composition results in prevention of development of cancer of the small intestine or colon, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

At page 21, while describing the rejection, Applicants point to the use of the word "enable" in the sentence in the rejection that states, "[f]urthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Applicants state that "the office seems to be discussing "enablement" based on the bolded term above, not written description.

Applicants' arguments have been fully considered but are not found persuasive. This solitary use of the word "enable" in a written description rejection does not render the rejection an "enablement" rejection rather than a written description. The use of "enable" in this sentence was used as part of a characterization of the state of the prior

art; in other words, if the prior art did provide compensatory teachings that enable the skilled artisan to identify the encompassed molecules, such teachings would support written description of the claimed genus. Applicants do not appear to dispute the substance of said statement.

New Claim Objections

Claims 10 and 11 are objected to because of the following informalities:

(1) In claims 10 and 13, the term "Hedgehog protein" is missing an article (e.g., "the"). Compare claims 10 and 13, which recite "…the source Hedgehog protein is…" with claim 12, which recites, "…the source of the Hedgehog protein is…"

Appropriate correction is required.

New rejections necessitated by Applicants' amendment

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-13 and 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the elements recited in the claims do not constitute proper Markush groups. Claim 1 is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
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